# Potential Applications of Pharmacogenomics to Heart Failure Therapies

Kishan S. Parikh, MD[a,*], Tariq Ahmad, MD, MPH[a,b], Mona Fiuzat, PharmD[a,b]

**KEYWORDS**

• Pharmacogenomics • Pharmacogenetics • Heart failure • Personalized medicine

**KEY POINTS**

- Pharmacogenomics refers to polymorphisms within the genome that may modify the individual response to treatment.
- Anywhere between 20% and 95% of the variability of a drug's response can be caused by genetic effects.
- Traditional heart failure management based on large, randomized trials and pharmacogenomics can form a complementary relationship to outline specific therapeutic options among a predefined patient population.
- Possible uses for pharmacogenomics in heart failure range from specific disease conditions, including pulmonary hypertension (PH), to optimization of well-established therapies, such as β-blockers and implantable cardiac defibrillators.
- Although the field is growing rapidly, pharmacogenomics in heart failure is still quite young and not quite ready for clinical application at the moment.

## BACKGROUND

Pharmacogenomics refers to polymorphisms within the genome that may modify an individual response to treatment, and the field has evolved alongside modern medicine. Although not equipped with the genetic knowledge of modern day, Sir William Osler[1] observed in 1892 that decompensation of patients with heart failure (HF) occurs at different rates, bringing attention to the heterogeneity with which the syndrome manifests.[1,2] A few decades later, in 1923, the English physiologist Archibald Garrod[3] noted that genetic variation may lead to variability in accumulation of both endogenous and exogenous products, including drugs.[3] With the help of the human genome project and genome-wide association studies (GWAS) over the last few decades, these basic concepts have propelled significant advances in therapies for oncology and infectious disease and have brought a better understanding of how best to dose cardiac therapeutics, such as antiplatelet agents and warfarin. Indeed, it is estimated that anywhere between 20% and 95% of the variability of a drug's response can be caused by genetic effects.[4]

On first glance, the idea of personalized medicine stands in stark contrast to the modern management of HF, which has been molded by large, randomized clinical trials comparing the effects of rival therapies on a single, phenotypically similar population.[5] Pharmacogenomics instead explores one drug's varying effects on different patient genotypes. However, the overall objectives of both

Disclosures: none.
[a] Division of Cardiology, Duke University Medical Center, 3428, Durham, NC 27710, USA; [b] Duke Clinical Research Institute, DUMC Box 3356, Durham, NC 27710, USA
* Corresponding author.
*E-mail address:* kishan.parikh@duke.edu

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are complementary and together can effectively outline an optimal algorithm for therapy (including drug, dose, duration, safety, and efficacy) in a predefined HF population. The utility of pharmacogenomics in HF will likely also increase, as drug regimens become more complex and new pharmacologic interactions and dosing considerations surface.

A better understanding of genomic variation's contribution to drug response can impact 4 arenas in HF: (1) identification of patients most likely to receive benefit from therapy, (2) risk stratify patients for risk of adverse events, (3) optimize dosing of drugs, and (4) steer future clinical trial design and drug development (**Fig. 1**).[4] Although the body of literature for pharmacogenomics of HF therapies is quite young, the field has already made initial significant advances and shows great promise.[6,7] In this review, the authors explore potential applications of pharmacogenomics in patients with HF in the context of these categories.

## THE UNMET NEED FOR OPTIMIZATION OF HF DRUG REGIMEN

HF is a public health problem of massive proportions in both developed and developing countries: In the United States alone, more than 5 million patients are estimated to have HF, more than 1 million hospitalizations and 270,000 deaths result annually from HF, and disease management accounts for more than $30 billion in total costs per annum.[8] However, evidence-based therapies, such as β-blockers and renin-angiotensin-aldosterone system (RAAS) inhibitors, that can significantly improve outcomes in HF continue to be used at doses far less than their thresholds for therapeutic efficacy. In part, this practice is a result of significant interpatient variation in what defines an optimized medical regimen, likely a function of genetic variation, patient behavior, and disease state.

Achieving an optimized medical regimen is critical to establish the best potential for recovery of ventricular function and is also becoming more complex as more options arise with new drugs and therapeutic combinations for different patient populations.[9] Fine-tuning the correct dose and balance of medications for patients can be challenging and traditionally has depended on several components, including patient tolerance, cost, compliance, and comorbid conditions. Frequently, several medications with proven mortality benefit in HF must be compared with each other during titration and selected in order of efficacy for initiation/dose increase. Preference given to one medication relies in part on the physician's gestalt because it cannot be known how well the theoretic benefit based on prior studies matches the patients' response to the drug. With an understanding of variability in drug response, whether a patient is more likely to have an adverse effect or have the desired response can be known before starting the drug. β-blockers, aldosterone antagonists, and angiotensin-converting enzyme inhibitors are among the most commonly used drugs in HF and have been examined for a genetic basis to explain patients' heterogeneous responses. In a short period of time, significant advances in pharmacogenomics have laid the groundwork for significantly improving HF management.

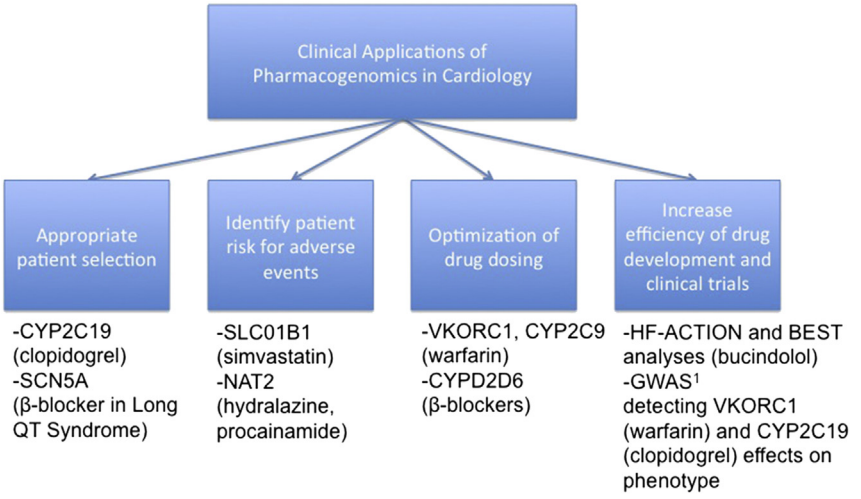


**Fig. 1.** Four broad arenas for potential pharmacogenomic use in cardiology have been established but require further exploration. [1] GWAS, genome-wide association study.